

AIC649 in Combination with Entecavir Leads to WHsAg Loss in the Woodchuck Animal Model of Chronic Hepatitis B

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INTRODUCTION

AIC649 is an inactivated parapoxvirus ovis particle preparation. It has been shown to directly address the antigen presenting cell arm of the host immune defense leading to a regulated cytokine release and activation of T cell responses.

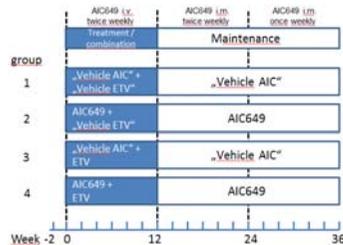
In the woodchuck animal model of chronic hepatitis B, intramuscular treatment with the immunomodulator AIC649 for 8 weeks has been shown to induce a unique bi-phasic response pattern, with reduction of woodchuck hepatitis virus (WHV) DNA and surface antigen (WHsAg) [Paulsen (2015)].

OBJECTIVE

In the present study, the antiviral activity of AIC649, alone or in combination with Entecavir (ETV), as well as different dosing routes and longer treatment periods were explored in chronically WHV-infected woodchucks. The objective was to further explore the safety and potential of AIC649 to induce a functional cure in chronic hepatitis B virus infection.

METHODS

In woodchucks, over a 36-week period, AIC649 was administered i.v. and then i.m., alone or in combination with an initial 12 weeks of the direct acting antiviral, ETV, given orally.



The efficacy of AIC649 monotherapy, ETV monotherapy, or combination AIC649 + ETV therapy was compared to a placebo control group (N = 5 animals / group). Treatment-induced changes in viremia, antigenemia, immunological parameters, as well as the induction of WHsAg antibody seroconversion were evaluated for determination of antiviral effects. Daily observations, changes in body weight and body temperatures, changes in hematology and clinical chemistry, as well as necropsy and histopathology were assessed for determination of safety.

RESULTS

Fig 1 – AIC649 suppresses WHV DNA

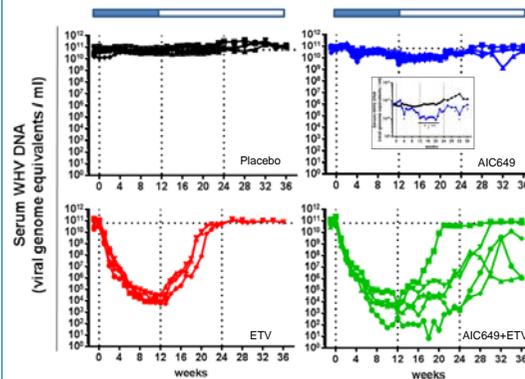


Fig 3 – AIC649 stimulates CMI responses

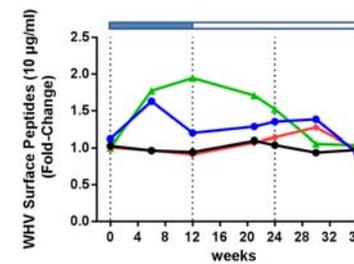


Fig 4 – AIC649 induces anti-WHsAg antibodies

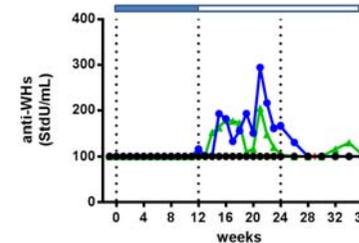


Fig 2 – AIC649 leads to WHsAg loss

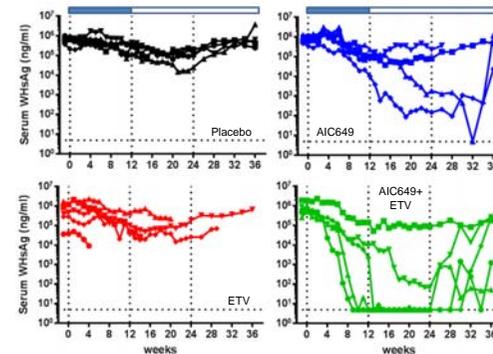
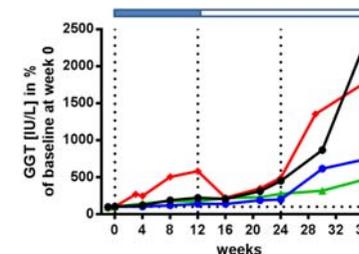


Fig 5 – AIC649 suppresses rise in GGT activity



Antiviral efficacy (fig 1+2), immunological responses (fig 2+3) and changes in liver parameter (fig 5) of AIC649 alone or in combination with ETV in chronically WHV infected woodchucks. Fig 1+2: Data from individual animals. Fig 1 small box and 3-5: Geometric means of the respective group, (fig 3: fold-change from baseline.; fig 5: normalized to baseline)

— „Vehicle AIC“ + „Vehicle ETV“
— AIC649 + „Vehicle ETV“
— ETV + „Vehicle AIC“
— AIC649 + ETV

SUMMARY

The bi-phasic response pattern induced by AIC649 monotherapy previously observed (Paulsen (2015)) was confirmed. Treatment with AIC649 alone already led to a clear reduction of WHV DNA as well as WHsAg from pretreatment levels. A significant and even stronger and sustained antiviral effect was observed in the AIC649 + ETV combination group: WHV DNA and WHsAg stayed markedly suppressed or even undetectable for several months in responding animals. Cell mediated immune responses, as well as anti-WHsAg antibody response, were observed in the two groups receiving AIC649 but not in the ETV monotherapy group. The changes in most of the liver disease markers were comparable between the groups, but the progression of steatosis and the increases in GGT during the study appeared slower in the AIC649 alone and the AIC649 + ETV combination group. Further analyses of immunological parameters as well as safety are still ongoing.

CONCLUSION

The observed sustained loss of WHsAg and the induction of anti-WHsAg antibodies accompanied by cell mediated immune responses support the hypothesis of AIC649 inducing a physiologically “concerted”, reconstituted immune response to WHV. AIC649 as a combination partner to ETV dramatically increases the efficacy of treatment. AIC649’s potential for inducing a functional cure in HBV-infected patients is supported by this preclinical study.

DISCLOSURES

This project has been funded in part with the pre-clinical services program from the Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN2722010000111, Task Order HHSN2720004 to Georgetown University (Stephan Menne). Tamara Pfaff, Ibironke Addy, Andreas Urban and Daniela Paulsen are employees of AiCuris Anti-infective Cures GmbH.